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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,936	KAMINSKI, JOSEPH M.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *2-4,10-14,17,19,22 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9,15,16,18,20,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Claim(s) 1-26, drawn to a nucleic acid comprising a transgene flanked by two terminal repeats and a nucleic acid encoding an integrating enzyme under the control of a promoter element.

Applicant's response to the Requirement for Restriction, filed on February 12, 2008 is acknowledged.

Applicant has elected the following species, wherein:

i) the promoter element species is an inducible promoter, specifically a tetracycline-responsive promoter, as recited in Claims 5-6.

ii) the integration enzyme species is transposase, specifically piggyBac transposase comprising a host-specific DNA binding domain fused to the N-terminus of the transposase, as recited in Claims 7, 9, 15 and 18,

iii) the nucleic acid composition species encoding the transgene and the nucleic acid encoding the transposase are the same nucleic acid, as recited in Claim 21, and

iv) the additional alternative element species is a homologous sequence that is homologous to the host DNA, as recited in Claim 23.

Election of Applicant's species was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

In the reply filed February 12, 2008, Applicant has amended Claims 1, 6, 9, 14 and 18-19.

Claims 2-4, 10-14, 17, 19, 22 and 24-26 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 5-9, 15-16, 18, 20-21 and 23 are under consideration.

Priority

This application is a 371 of PCT/US03/23090 filed on July 24, 2003. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/398,628, filed on July 24, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Accordingly, the effective priority date of the instant application is granted as July 24, 2002.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on January 24, 2005, September 18, 2006, and April 17, 2008 that have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

The listing of references in the specification (pgs 97-109) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

Specification

Sequence compliance

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

1. **The disclosure is objected to for the following reason:** this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid

sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers.

Applicant's attention is drawn specifically to Figure 16 and pg 76, Table 3.

The specification is objected to because Figure 16 contains a nucleic acid sequence without a corresponding SEQ ID NO in the figure or figure legend. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier,("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP §2422.02.

It is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 244.02). If the sequences are already present in the sequence listing, it would be remedial to amend the Brief Description of the Drawings or specification to include the appropriate sequence identifiers. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive.

37 CFR 1.821(f) states that in addition to the paper copy required by paragraph (c) of this section and the computer readable form required by paragraph (e) of this section, a statement that the content of the paper and computer readable copies are the same must be submitted with the computer readable form, *e.g.*, a statement that "the information recorded in computer readable form is identical to the written sequence listing."

Note that if the SEQ.txt file was received via EFSWeb and the text file meets the requirements for the paper copy and CRF, no statement is required.

The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. **Claims 1, 5-9, 15-16, 18 and 20 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Handler et al (PNAS 95:7520-7525, 1998) in view of Kim et al (U.S. Patent 6,479,626), Katz et al (Virology 217:178-190, 1996) and Elledge et al (U.S. Patent 6,828,093).

Determining the scope and contents of the prior art, and Ascertaining the differences between the prior art and the claims at issue

Handler et al teach a composition comprising a first nucleic acid comprising a transgene flanked by two terminal repeats and a second nucleic acid encoding an integrating enzyme under the control of a promoter element. The first and second nucleic acids are separate plasmids (pgs 7520-7521, joining ¶, Plasmids; pg 7523, Figure 2A). The integrating enzyme is a transposase, more specifically from piggyBac. Given that the piggyBac transposase is on a separate plasmid from the first nucleic acid molecule, the transposase is considered to be "located outside the terminal repeats" of the first nucleic acid.

Handler et al do not teach the integrating enzyme to be a chimeric integrating enzyme. However, at the time of the invention, Kim et al disclosed recombinant DNA-binding proteins which include zinc finger and helix-loop-helix motifs (see abstract and introduction). The chimeric zinc finger proteins of the invention are composed of two or more DNA-binding domains, where at least one of the DNA binding domains is a zinc finger polypeptide. The second DNA binding domain can be a zinc finger binding domain, either the same domain or a heterologous domain. The second DNA binding domain can also be a heterologous host-specific DNA binding domain, e.g., from a restriction enzyme; a nuclear hormone receptor; a homeodomain protein or a helix turn helix motif protein (col. 6, lines 28-45) and comprise a regulatory domain that has a DNA modifying activity such as found in integrases and recombinases (col. 10, lines 54-63). Expression of the chimeric proteins can be controlled by systems typified by the inducible tetracycline-regulated systems (col. 6, lines 62-64; col. 17, lines 44-49).

Kim et al do not disclose the host-specific DNA-binding domain to be fused to the N-terminus of the transposase. However, at the time of the invention, Katz et al taught a chimeric integrating enzyme, wherein the DNA-binding domain of LexA is fused to the catalytic domain of integrase, wherein the LexA DBD was present at the N-terminus of the fusion protein (pg 181, col. 1, ¶2).

Neither Kim et al nor Katz et al teach that the genus of integrases and recombinases embrace transposases. However, at the time of the invention, Elledge et al disclosed that site-specific recombinases refers to enzymes that recognize short DNA sequences that become the cross-over regions during the recombination event and includes recombinases, transposases and integrases (col. 17, lines 15-19). Thus, at the time of the invention, piggyBac transposase was an art-recognized species within the genus of site-specific recombination enzymes comprising transposases, integrases and recombinases.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the

practical experience in molecular biology, recombination cloning, and the creation of transgenic cells and organisms using transposable elements. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to modify the piggyBac transposase to comprise a heterologous host-specific DNA-binding domain with a reasonable chance of success because the prior art (e.g. Katz et al) had successfully demonstrated that the catalytic recombination activity of site-specific recombination enzymes were functional when operably linked to a heterologous DNA-binding domain. An artisan would be motivated to modify the piggyBac transposase to comprise a heterologous host-specific DNA-binding domain because Kim et al disclose that the heterologous design allows one to increase the affinity of the DNA binding polypeptide for its target DNA (see introduction) and Katz et al teach that the integrating enzymatic activity may be influenced or enhanced by fusion to a heterologous DNA-binding domain so as to enhance or target integration at a desired target site (pg 179, col. 1, ¶2-3). Katz et al suggest that such a chimeric fusion strategy may be useful for targeting or enhancing integration of a nucleic acid vector *in vivo* (pg 189, col. 1, ¶1; col. 2).

It also would have been obvious to substitute the promoter operably linked to the piggyBac transposase with a tetracycline-inducible promoter with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute the promoter operably linked to the piggyBac transposase with a tetracycline-inducible promoter because the tetracycline-inducible system has long been recognized to provide the artisan with significant transcriptional control over the timing and expression level of the desired gene expression product.

Thus, the invention as a whole is *prima facie* obvious.

5. **Claims 20-21 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Handler et al (PNAS 95:7520-7525, 1998) in view of Kim et al (U.S. Patent 6,479,626), Katz et al

(Virology 217:178-190, 1996) and Elledge et al (U.S. Patent 6,828,093), as applied to claims 1, 5-9, 15-16, 18 and 20 above, and in further view of Grigliatti et al (U.S. 2002/0116723).

Determining the scope and contents of the prior art

Neither Kim et al, Katz et al nor Elledge et al teach the first nucleic acid comprising a transgene flanked by two terminal repeats and the second nucleic acid encoding an integrating enzyme under the control of a promoter element to be the same nucleic acid molecule, wherein the integrating enzyme is located outside the terminal repeats. However, at the time of the invention, Grigliatti et al disclosed transposon-based transformation vectors comprising the use of transposase, e.g. piggyBac [0229], wherein the transposon vector comprises terminal repeats, and wherein the transposase gene and heterologous protein expression cassette are within the transposon termini [0026]. While the transposase is expressed, the enzyme directs the entry of the transposon into the genomic DNA. Transposase expression may be modulated to regulate the movement of the transposon, thereby controlling transposon copy number [0025].

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, recombination cloning, and the creation of transgenic cells and organisms using transposable elements. Therefore, the level of ordinary skill in this art is high.

Ascertaining the differences between the prior art and the claims at issue, and Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to combine the first nucleic acid comprising a transgene flanked by two terminal repeats and the second nucleic acid encoding an integrating enzyme under the control of a promoter element in the same nucleic acid molecule with a reasonable chance of success because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common

sense.", and all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. There are only two formal possible combinations between the first and second nucleic acid molecules, either they are within the same nucleic acid molecule or are in separate nucleic acid molecule. An artisan would be motivated to combine the first nucleic acid comprising a transgene flanked by two terminal repeats and the second nucleic acid encoding an integrating enzyme under the control of a promoter element in the same nucleic acid molecule because it is but one of two possible choices and the art recognizes that both permutations will achieve transposition of the desired heterologous nucleic acid.

Grigliatti et al do not disclose that the transposase would be positioned outside the terminal repeats of the transposon. However, it would have been obvious to one of ordinary skill in the art to try positioning the transposase outside the terminal repeats of the transposon when the first nucleic acid comprising a transgene flanked by two terminal repeats and the second nucleic acid encoding an integrating enzyme under the control of a promoter element are the same nucleic acid molecule because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." There are only two possible placements of the nucleic acid molecule encoding the transposase: either within or outside the terminal repeats. Given the art-recognized mechanism of transposition, those nucleic acids within the terminal repeats will be integrated into the host cell genome; whereas, those nucleic acids outside the terminal repeats will not integrate. An artisan would be motivated to to try positioning the transposase outside the terminal repeats of the transposon when the first nucleic acid comprising a transgene flanked by two terminal repeats and the second nucleic acid encoding an integrating enzyme under the control of a promoter element are the same nucleic acid molecule so as to establish stable integration of the desired transgene.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

6. **Claim 23 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Handler et al (PNAS 95:7520-7525, 1998) in view of Kim et al (U.S. Patent 6,479,626), Katz et al (Virology

217:178-190, 1996) and Elledge et al (U.S. Patent 6,828,093), as applied to claims 1, 5-9, 15-16, 18 and 20-21 above, and in further view of McFarlane et al (Transgenic Res. 5(3):171-177, 1996; Abstract only).

Determining the scope and contents of the prior art

Neither Kim et al, Katz et al, Elledge et al nor Grigliatti et al disclose the nucleic acid composition to further comprise a homologous sequence that is homologous to the host DNA. However, at the time of the invention, McFarlane et al taught the inclusion of a nucleic acid sequence having 5 base pairs that were homologous to the host DNA. McFarlane suggest that this feature was likely to have been factorial in the insertion event, and propose a model depicting a mechanism by which precise integration may occur.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, recombination cloning, and the creation of transgenic cells and organisms using transposable elements. Therefore, the level of ordinary skill in this art is high.

The Examiner notes that the claim does not specify either the minimal length or the location of the sequence that is homologous to the host DNA, and at present a single nucleotide anywhere in the nucleic acid(s) would reasonably fulfill the instantly claimed limitation.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to combine a homologous sequence that is homologous to the host DNA with a nucleic acid composition comprising a transgene flanked by two terminal repeats and a nucleic acid encoding an integrating enzyme under the control of a promoter element with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the

combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine a homologous sequence that is homologous to the host DNA with a nucleic acid composition comprising a transgene flanked by two terminal repeats and a nucleic acid encoding an integrating enzyme under the control of a promoter element because at the time of the invention, those of ordinary skill in the art had long recognized that the inclusion of nucleic acid sequences homologous to the host DNA would significantly improve the likelihood that the transformation vector would integrate at a desired location in the host genome. Such has been standard practice for the generation of transgenic mice.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

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